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Review—Non-Invasive Monitoring of Human Health by Exhaled Breath Analysis: A Comprehensive Review

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Exhaled human breath analysis is a very promising field of research work having great potential for diagnosis of diseases in non-invasive way. Breath analysis has attracted huge attention in the field of medical diagnosis and disease monitoring in the last two decades. VOCs/gases (Volatile Organic Compounds) in exhaled breath bear the finger-prints of metabolic and biophysical processes going on in human body. It's a non-invasive, fast, non-hazardous, cost effective, and point of care process for disease state monitoring and environmental exposure assessment in human beings. Some VOCs/gases in exhaled breath are bio-markers of different diseases and their presence in excess amount is indicative of un-healthiness. Breath analysis has the potential for early detection of diseases. However, it is still underused and commercial device is yet not available owing to multiferrious challenges. This review is intended to provide an overview of major biomarkers (VOCs/gases) present in exhaled breath, importance of their analysis towards disease monitoring, analytical techniques involved, promising materials for breath analysis etc. Finally, related challenges and limitations along with future scope will be touched upon.

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Exhaled breath analysis an important area of research work which has gained tremendous interest recently owing to the advances in analytical techniques and nanotechnology. This is a non-invasive method for disease detection, therapeutic monitoring, and metabolic status monitoring by analyzing the volatile organic compounds (VOCs) present in the exhaled breath. Along with point of care detection breath analysis has the advantage of non-invasive, cost-effective, real time, qualitative/quantitative disease diagnosis[1–3] and hence it has the potential of replacing traditional blood test which is invasive and pain-staking. Alongside exhaled breath VOCs are also emitted from urine, sputum and faces[1] (all non-invasive in nature) also but breath is easiest of all these to handle and hence has the obvious edge over the other clinical sample.

Exhaled breath analysis for disease diagnosis is an ancient practice: even in the time of Hyppocrates this was in vogue. Sweet breath odor was linked with diabetes and fish-like smell in exhaled breath was identified with kidney-related diseases.[4] In the late 1780s Lavoisier took the first initiative to determine the chemical components of human breath. In 1971 Linus Pauling demonstrated that breath is a complex gas containing no less than 200 VOCs and this for sure marked the beginning of the modern breath testing.[5] Later, Michael Phillips demonstrated that breath contains more than 300 VOCs.[6] Now it is known that breath contains more than 3500 VOCs.[7]

Human exhaled breath mostly contains, nitrogen (78.04%), oxygen [16%], carbon dioxide [4%-5%], hydrogen [5%],[8] inert gases [0.9%][9] and water vapor. Other than that, it contains inorganics VOCs viz. nitric oxide (10–50 ppb),[10] nitrous oxide (1–20 ppb),[10] ammonia (0.5–2 ppm),[11] carbon monoxide (0–6 ppm),[9] hydrogen sulphide (0–1.3 ppm)[12] etc. and organic VOCs such as acetone (0.3–1 ppm),[13] ethanol, isoprene (∼105 ppb),[14] ethane (0–10 ppb), methane (2–10 ppm), pentane[0–10 ppb][10] etc. The air that is inhaled goes into the alveoli in the lungs where the metabolic excretable products diffuse into the inhaled air and then it is rejected in the form of exhaled air. Therefore, the exhaled air must carry the fingerprint of the metabolic process going on endogenously. Hence it is a rich source for disease diagnosis and health monitoring. As such the principle of breath analysis is thus simple. However, it is fraught with challenges that makes it complex. Firstly, a healthy human being exhales around 500 ml of breath out of which 150 ml is dead space air which comes from the upper air tract; this does not exchange VOC/gas with the blood and therefore acts as a diluent only.[15,16] Secondly, many of the exhaled breath VOCs/gases are partially or fully of exogenous in origin[17,18] and depends on ambient air concentration, duration of exposure, solubility and partition co-efficient, mass and fat content of the individual etc. Thirdly, non-volatile components such as isoprostanes, peroxynitrite etc, present as aerosol in breath can be measured only from breath condensate.[19] Fourthly, oral hygiene is a problem for many people. Finally, it is very difficult to detect a particular VOC with very low concentration (ppm/ppb) among thousand others. In addition, age, gender, food habit and pregnancy in case of women affects the breath composition.[20–24] Furthermore, there are no standards for breath collection techniques. In spite of all these challenges breath analysis is much easier than blood testing and therefore has attracted the attention of researchers in recent times.

In this review we will discuss the different techniques for the detection of breath biomarkers with a focus on semiconducting materials and their mechanism of gas sensing. It is in this context that we will also discuss the metabolic pathways for the generation of different breath biomarkers and their connection with different diseases; breath collection, preconcentration, desorption and storage; nanomaterials and sensor arrays for the detection of different cancers and finally the potential and plausible future of breath research. Indeed, there are multiple reviews in this topic but one must understand that this is a rapidly growing field of research. Righettoni et al.[25] reported that since the year 2000, ∼140000 research papers have been published only on the topic of breath analysis itself. Therefore, comprehensive reviews must come up every year so as to keep the researchers around the globe informed about the recent progresses in the field.

Diseases and Disorders Indicated by Important Biomarkers

The most important biomarkers of diseases in human body are ammonia, acetone, isoprene, nitic oxide, hydrogen sulphide, methane, ethane and pentane. In this section we will discuss the metabolic pathways of removal of these biomarkers and also will delineate in short, the diseases indicated by those when excreted in less or excess amount through the exhaled breath.

Ammonia (NH_3).—Ammonia has essential nutritional values for human body, viz. synthesis of purines and pyrimidines, amino sugar

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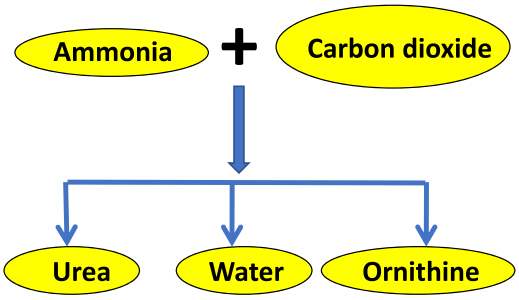

Figure 1. Elimination of excess ammonia from human body in the form of urea.

synthesis, maintaining the acid-base balance in the blood and producing non-essential amino acids in the body. However, excess ammonia in the body acts as toxin. Therefore, excess ammonia is removed from the body by urea cycle or ornithine cycle that converts ammonia into urea which is excreted in the form of urine through kidney. Figure 1, briefly shows the urea cycle.[26–28] This cycle takes place in liver and kidney. Therefore, if there is a problem in the liver or renal functioning it is reflected in an increased concentration of ammonia in exhaled breath, as a part of it is also excreted through breath.

Increased breath ammonia indicates several diseases, viz. kidney failure, liver dysfunction,[29] hepatic encephalopathy, swelling of brain, type-II Alzheimer's disease[30] etc. Increased ammonia in exhaled breath may also indicate peptic ulcer and halitosis.[31–34] In asthma patients however, breath ammonia concentration decreases.[35]

The average ammonia concentration in healthy individuals is approximately 250 ppb.

Nitric oxide (NO).—Nitric oxide (NO) has a critical role to play in the cell-signaling and its increased concentration in breath may be indicative of the pathophysiology of many diseases.[36,37] A large concentration of NO in exhaled breath is correlated with asthma. During asthma voluminous amounts of NO are produced in the airway by inducible-NOS (i-NOS). A healthy human being contains less than 25 ppb NO in breath, whereas in asthmatic patients it goes beyond 50 ppb.[38] Other than asthma, increased release of NO in human breath can be indicative of liver transplant rejection, chronic pulmonary obstructive disease and cystic fibrosis.[39–42]

Hydrogen sulphide.—Hydrogen sulphide is a well-known toxic gas with a malodor. It is a significant gasotransmitter in humans and animals signaling multiple physical processes such as, neuromodulation, cytoprotection, inflammation, apoptosis, vascular tone regulation etc.[43–48] Hydrogen sulphide may act as the biomarker of asthma,[49] airway inflammation,[50,51] and also oral and dental heath.[52] The hydrogen sulphide concentration in healthy individuals ranges form 8–16 ppb.

Acetone.—Acetone was first recognized as the breath-biomarker of diabetes by Petters in 1857.[53,54] It should be understood clearly that glucose is the main source of energy in human body. Insulin allows glucose molecules to be absorbed in the cells. In case there is insufficient insulin generation by the body (Type-I diabetes) or insulin-resistance of the cells (Type-II diabetes) body is unable to extract energy from glucose and is compelled to break body fat to produce energy. Ketogenesis is one of such pathways. Ketogenesis is the source of all ketone bodies including acetone in humans. Figure 2 shows the basic steps involved in ketogenesis. Breath acetone concentration increases as the severity of diabetes in a patient escalates. The relation between blood and breath acetone is linear (acetone in exhaled air is approximately 1/330 times the acetone in plasma). For a non-diabetic person the breath acetone level is $\leqslant$0.9 ppm, for a moderately diabetic patient it is 0.9 ppm to 1.8 ppm and for seriously diabetic patients it can be several tens of

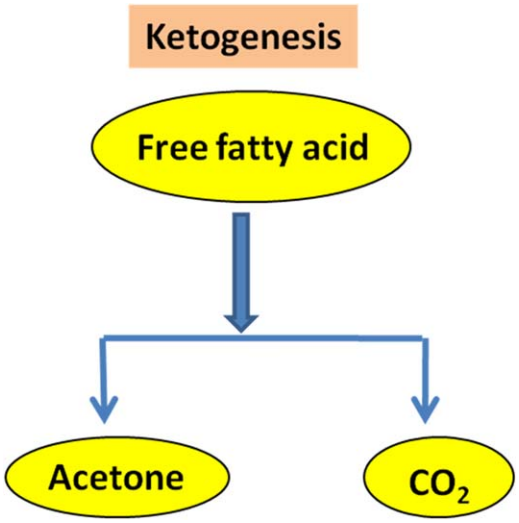

Figure 2. Production of acetone in human body by ketogenesis from free fatty acids.

ppm. Breath acetone level also increases in diabetic ketoacidosis, starvation, physical exercise and high fat/ketogenic diet.[55,56]

Isoprene.—Isoprene is present copiously in human breath. Isoprene, along with acetone acts as the biomarker of diabetes. Isoprene is a byproduct of cholesterol production in body and hence it can be potentially used as the biomarker for lipid metabolism disorder,[8,57,58] such as, anesthesis. When the concentrations of acetone, isoprene and methanol in breath are collectively lower than normal it might indicate lung cancer.[14] The concentration of isoprene in the breath of a healthy individual is approximately 105 ppb.

Methane, ethane, pentane.—Human bodies can not generate methane by themselves and Methanogenic bacteria (e.g. *Methanobrevibacter Smithii*) present in human intestine produces methane in anaerobic condition. Generally, methane is not present in human breath but in case of presence of excess methane generation it appears in the faeces and then it can also be detected in human breath also. The diseases caused by excess or less of methane in human body are obesity, irritable bowel syndrome, inflammatory bowel diseases, anorexia etc. Pentane and ethane are produced by the oxidation of cellular lipids.[59] Excess ethane in exhaled breath may be caused by oxidative stress, vitamin E deficiency, breast cancer, ulcerative colitis, whereas pentane in exhaled breath can be indicative of oxidative stress, physical and mental stress, arthritis, breast cancer, asthma, COPD, inflammatory bowel diseases, sleep apnea, ischemic heart disease, myocardial infraction, liver disease, schizophrenia, sepsis etc.[60–69]

Aldehydes.—Endogenous alkenals, hydroxyalkenals, and dialdehyde products of lipid peroxidation (LPO) tend to increase in cancer patients. LPO is a process where polyunsaturated fatty acids are peroxidised by free radicals and aldehydes could be reaction products. Patients with Wilson's disease, hemochromatosis associated with liver cancer, childhood cancer, alcoholic liver disease, smoking, oxidative stress, diabetes and atherosclerosis tend to have increased aldehyde levels in blood and breath.[70] Metabolic and/or genetic disorders in the synthesis and metabolism of aldehydes, such as, glyoxal, methylglyoxal, formaldehyde, semialdehydes etc. may lead to diabetes, hypertension, aging, Cerebral Ischemia,[71,72] Alzheimer's Disease (AD) and Parkinson's Disease (PD),[73] Amyotrophic Lateral Sclerosis (ALS) or Lou Gehrig's Disease,[74] Wernicke's Encephalopathy, lung cancer etc. When the concentration of such aldehydes increases in blood and urine it's concentration in exhaled breath is also elevated. Thus, it can act as biomarker of multiple diseases, especially lung cancer.

Table I lists the major breath biomarkers along with the diseases they indicate.

Techniques of Detecting Breath Biomarkers in Gas Phase

It is clear form the above discussions that human breath is a rich mixture of VOCs acting as biomarkers for different diseases and metabolic disorders. Therefore, detection of such VOCs in human breath can lead to potential non-invasive detection of diseases. In the following subsections we will discuss different methods developed to date to detect VOCs in very low concentrations (ppm_v, ppb_v and ppt_v). Table I summarises the major diseases related to VOC biomarkers.

Chromatographic and spectroscopic techniques.— *Gas chromatography (GC).*—Chromatography is a method where a mixture of molecules of different compounds is forced by a carrier gas (generally He) through a column that separates the molecules[75] and the separated molecules are detected by a detector (ref. Fig. 3). In the last one decade or so, researchers across the globe are using GC combined with different kinds of detectors to detect breath VOCs for the purpose of disease detection and health monitoring. Sanchez et al.[76] detected about 25 components of human breath including important biomarkers such as, acetone, ethanol, isoprene, methanol, pentane using a series couple column ensemble [polar column stationary phase trifluoropropylmethylpolysiloxane or poly(ethylene glycol) and non-polar column stationary phase dimethyl polysiloxane] in combination with four-bed sorption trap and a flame ionization detector. The detection limit was 1–5 ppb in 0.8L of breath. Lord et al.[77] developed a GC-IMS based analytical system that could detect breath acetone and ethanol and obviated the effect of breath moisture to a large extent. Giardina et al.[78] developed a low temperature glassy carbon based solid-phase mass extraction microfiber that were capable of extracting five cancer related breath VOCs from simulated breath and the extracts were analyzed by GC/MS with good sensitivity. Phillips et al.[79] used GC-FID and GC-FPD (GC-flame photometric detection) techniques combined with a novel breath collection and preconcentration device to quantitatively detect isoprene from human breath with sufficient sensitivity, and accuracy. Lamote et al.[80] used GC-MS and e-Nose to differentiate between Malignant pleural mesothelioma (MPM) patients and asymptomatic asbestos-exposed person at a risk of the said disease. Schnabel et al.[81] employed GC-TOF-MS to show non-invasive detection of ventilator associated pneumonia (VAP) in ICU patients by breath VOC analysis and they identified 12 VOCs for that purpose. Beccaria et al.[82] employed thermal desorption-comprehensive two-dimensional gas chromatography-time of flight mass spectrometry methodology and chemometric techniques to detect pulmonary tuberculosis by analyzing exhaled breath VOCs. GC-MS was also employed by Durán-Acevedo et al.[83] to differentiate between healthy individuals and patients of gastric cancer by breath analysis using GC-MS. There are also other examples of such GC based breath analysis.

Proton transfer reaction mass spectrometry (PTR-MS).—PTR-MS is also a tool of analytical chemistry.[84] Classical PTR-MS uses gas phase hydronium ion as ion (purity >99.5%) source reagent. Using this technique absolute concentration of the target VOCs can be measured without calibration, the detection limits could be as low as ppt_v. Figure 4 shows the block diagram of a PTR-MS. PTR-MS owing to its excellent sensitivity and specificity can be used for breath gas analysis to monitor the physiological and pathophysiological conditions of human subjects. Amann et al.[85] employed PTR-MS to investigate the variation in concentration of various VOCs during sleep (long-time, online monitoring combined with polysomnography), in patients with carbohydrate malabsorption (major role played by gut bacteria), and intra and inter-subject variability of one particular mass. Karl et al.[86] used PTR-MS to determine the level of isoprene in exhaled breath to detect cholesterologenesis from exhaled breath. Lirk et al.[87] observed that potentially it is possible to screen head and neck squamous cell carcinoma using PTR-MS on exhaled breath VOCs using few biomarkers such as, isoprene. Boschetti et al.[88] reported to have simultaneously monitored a large number of VOCs in real time and with high sensitivity (tens to few ppt_v).

Selected mass flow tube mass spectrometry (SIFT-MS).—SIFT-MS is a tool of analytical chemistry for the quantitative detection of trace VOCs.[89] Reagent ions, viz, H_3O^+, NO^+, O_2^+ etc ionize the gas/VOC samples which are further quantified by a quadrupole mass spectrometer. Figure 5 shows the block diagram of a SIFT-MS. It was first developed to detect the trace VOCs present in human breath for prognosis of disease and to monitor physiological and pathophysiological conditions. Spanel et al.[90] used SIFT-MS and O_2^+ reagent ions to quantitatively detect isoprene in human breath. Diskin et al.[91] studied the variation in concentration of common breath biomarkers, such as ammonia, isoprene, ethanol, acetaldehyde and acetone over a period of 30 days using SIFT-MS with 5 healthy individuals. Abbott et al.[92] quantified acetonitrile from exhaled breath and urinary head space of many smokers and non-smokers. Vaira et al.[93] studied the relation between *Helicobacter pyroli* concentration in the gut with gastrointestinal disease, liver disease, extra-gastrointestinal conditions, gastro-esophageal reflux etc. In 1996 itself, Smith et al.[94] used SIFT-MS to demonstrate that the breath ammonia concentration of a known *Helicobacter pyroli* infected person increased by ~4 ppm after an oral dose of 2 g non-radioactive urea. Also, SIFT-MS was employed by Samara et al. (biomarker identified: acetone and pentane for acute decompensated heart failure), Cikach et al. (biomarker identified: isoprene and trimethylamine for acute decompensated heart failure), Alkhouri et al. (biomarker identified: acetone, isoprene, trimethylamine, acetaldehyde, pentane for non-alcoholic fatty liver disease), Hanouneh et al. (biomarker identified: 2-propanol, ethanol, acetone, trimethylamine, acetaldehyde, pentane for alcoholic hepatitis), Walton et al. (biomarker identified: acetone for diabetes mellitus), Storer et al. (biomarker identified: acetone for diabetes mellitus)[95–100] and many others to explore non-invasive detection of diseases from exhaled breath.

Nanomaterials for VOC detection.— *Semiconductor oxides.*—In the previous section we have discussed about the spectroscopic techniques for breath analysis. In comparison to those techniques metal oxide semiconductor-based sensors provide multiple advantages, viz. small size, low cost, ease of operation, low power consumption, minimum maintenance requirements and overall simplicity. Thus, progressively increasing number of research groups around the globe are engaging themselves in the development of new metal oxide semiconductor (MOS) based sensor systems capable of detecting breath biomarkers of different diseases in breath background at concentration levels as low as ppm_v, ppb_v or even ppt_v. To develop one such new composition it is important to understand the basic sensing mechanism of MOS sensors.

Gas sensing capability of MOS sensors completely depends on the change in electrical conductivity of the oxide material in response to the change in composition of the surrounding atmosphere. These sensors generally operate at high temperatures since oxide materials behave like insulators at room temperature, i.e. most of the electrons reside in the valence band and conduction band remains mostly empty. However, during synthesis defect bands are generated in the forbidden energy gap between the valence and conduction band. These defect bands could form either near the valence band as acceptor states or near the conduction band as donor states. The oxides having donor states are n-type MOS and those having acceptor states are p-type MOS. These defect states could have various origins, viz. defects in bulk oxide developed during synthesis process, high energy sites available in quantum dots, nanorods, nano sheets, nano tubes, nano belts and other exotic nanostructures, doping of novel and non-novel metals and oxides

Table I. Biomarker vs Disease.

Biomarker	Major disease	Maximum permissible limit
Ammonia	Renal failure, liver dysfunction, cirrhosis of liver, peptic ulcer, halitosis etc	250 ppb
NO	Asthma, COPD, Asthma like diseases, viz. Laboratory animal allergy, lung infections in aluminium pot-room workers, swine confinement workers, lung cancer etc	25 ppb
Hydrogen Sulphide	Asthma, Airway inflammation, oral malodor, dental disease etc	8–16 ppb
Acetone	Diabetes	0.9 ppm
Isoprene	Diabetes, hypercholesterolemia	105 ppb
Methane, ethane, pentane	Intestine and colon related disease, breast cancer, liver diseases, asthma etc	—
Aldehydes	Cancers, viz. lung cancer, breast cancer, Alzheimer's disease, Parkinson's Disease, Wernicke's encephalopathy etc	—

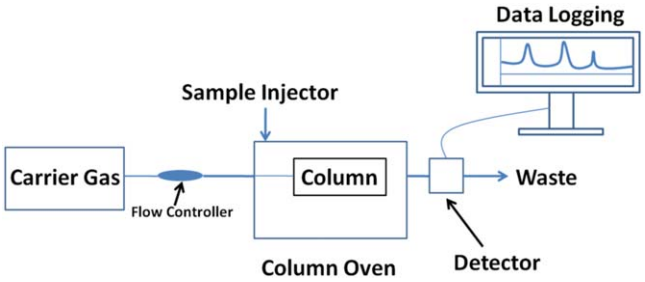

Figure 3. Block diagram of a Gas Chromatograph.

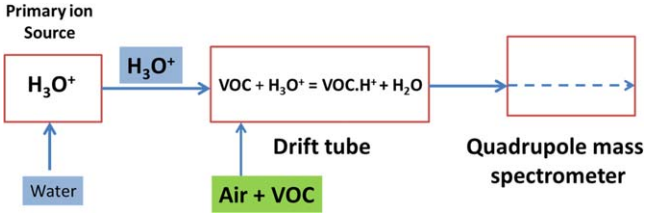

Figure 4. Block diagram of PTR-MS.

into the host lattice, band bending at the edges of particles in composite materials etc. At elevated temperatures (100 °C to 500 °C) electrons from the donor bands jump to the conduction band or from valence band to acceptor bands.[101] Ambient oxygen due to its electron affinity binds with these electrons and forms a variety of oxygen species with negative charges (O_2^-, O^-, and O^{2-}), thereby forming electron depletion layer (EDL) in n-type semiconductors and hole accumulation layer (HAL) in p-type semiconductors near the surface of the oxide.[102] When the surface is exposed to reducing gases such as NO_x, NH_3, acetone, alcohol, isoprene etc ionsorbed oxygen at the surface oxidizes these molecules and thus gets consumed itself. Thus, the electrons previously trapped by these oxygen molecules are reverted back to the EDL or HAL and thus the conductivity increases or decreases, respectively. Thereafter, the ambient oxygen molecules recreate the EDL or HAL at the surface. Just the opposite happens when the material is exposed to oxidizing gases and VOCs. In essence, MOS behaves as n-type or p-type semiconductor at the elevated temperature. When the sensor is exposed to reducing gases, the resistance decreases for n-type oxides and increases of p-type oxides. The opposite phenomenon takes place in case the gas or VOC is oxidizing, viz. CO_2. Equations 1–5 describe the aforementioned phenomena for n-type MOS sensors. For p-type MOS sensors just the opposite phenomenon takes place.

$$O_2(gas) = O_2(absorbed). \quad [1]$$

$$O_2(absorbed) + e^- = O_2^-. \quad [2]$$

$$O_2^- + e^- = 2O^-. \quad [3]$$

$$O^- + e^- = O^{(2-)}. \quad [4]$$

$$Reducing\ Gas + O_2^-/O^-/O^{(2-)} = CO_2 + H_2O + e^-. \quad [5]$$

From this brief discussion on the mechanism it is clear that the sensitivity of the sensors depends on the material composition, particle size, particle morphology, porosity of the sensor film, crystallographic planes exposed at the surface and film thickness. Doping and compositing the pristine material often increases sensitivity of the sensor. For example, surface modification of tin dioxide with palladium heightens the sensor response.[103–109] However, there is an optimum limit to that beyond which reduction in sensitivity is observed. Since the EDL and HAL forms at the surface itself, it is obvious that maximizing the surface area must increase the sensitivity, In thin films,[110,111] porous structures, 1-D[112] and 2-D[113] materials the exposed surface area is enhanced, therefore sensitivity increases significantly. Also, enhancing the reactivity at the surface will enhance sensitivity and that could be observed with 1-D, 2-D oxide particles and thin films.

Another important aspect of any sensor is selectivity. In general, the specificity of pristine oxide materials is not impressive. However, researchers have used various approaches to enhance selectivity, viz modulation of operating temperature,[114] noble-metal or oxide catalyst loading,[115,116] acid-base interaction between target gases/VOCs and the MOS,[117] reforming the target gases within the sensing layer,[118,119] interface-gas filtration[120] etc. The effect of some major parameters on sensitivity and selectivity are discussed in details in the latter part of this section.

Power consumption is a limitation of thick film MOS sensors. One of the major advantages of such sensors is that it could be used for making hand-held devices. A hand-held device is essentially battery operated. However, a standard thick film MOS sensor consumes about 0.5 W to 1 W power. Such power consumption is difficult to be sustained for prolonged times using batteries. Also, the current drawn by the circuit is of the order of 100–300mA which is quite high and requires sophisticated electronic circuitry to handle it. Also, during prolonged use it heats up the air in the vicinity and creates turbulence there. This hinders the streamlined flow of analyte gases onto the surface of the sensor, especially when breath gas analysis is concerned. It is difficult to get repetable results under such conditions. Lowering the operating temperature could be one solution but it comes with other allied problems such as, low selectivity, slow response and recovery, unstable base resistance etc. This necessitates the introduction of MEMS based thin film sensors which have higher sensitivity, lower resistance, lower power consumption and eventually consumes much less physical space. The advent of MEMS and NEMS based sensors also opens up the horizon to hand held sensor array-based devices. Sensor arrays are one of the best solutions to the selectivity issue of such sensors.

Following are some of the recently developed MOS sensors having the potential of being used in breath biomarker detection.

Tungsten oxide (WO_3) has been identified as a potential MOS for the detection of NO in ppm and ppb levels. Moon et al.[121] reported

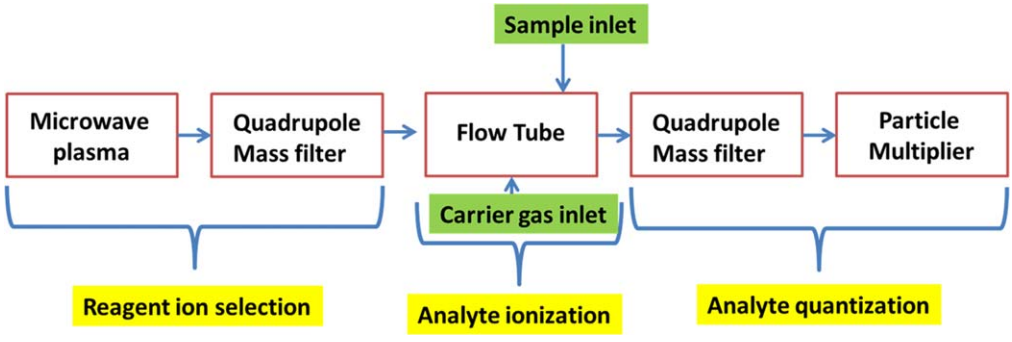

Figure 5. Block diagram of SIFT-MS.

that villi-like WO_3 is capable of detecting down to 200 ppb NO. Koo et al.[122] reported that nanotubes of WO_3 are capable of detecting 1 ppb NO in high humidity (>80%). Sun et al.[123] used sensor design with the adjacent alignment of p-type chromium oxide (Cr_2O_3) and n-type WO_3 to detect down to 18 ppb NO in presence of 20 ppm CO. Their study was even extended to detection of NO in human breath samples. Zhang et al.[124] observed the selective sensing of NO_2 by ZnO hollow spheres-based sensors. Gouma et al.[125] reported that γ-WO_3 is a selective NO sensor in presence of other breath volatiles, viz. acetone, isoprene, ethanol, CO and methanol. Fruhberger et al.[126] reported that WO_3 based sensor can detect down to 60 ppm NO when passed through an oxidizing filter of alumina supported potassium permanganate. However, it seems that far more studies have to be carried out in this regard. The detection of NO_x becomes difficult considering that NO_x is a common air pollutant. Also, NO_x concentration is very high in children (~450 ppb as compared to ~30 ppb in non-asthmatic adults). Therefore, it is difficult to detect asthma by detection of NO_x in exhaled breath in children. Furthermore, adults having stabilized asthma exhibits ~20–25 ppb NO_x in exhaled breath which is not so different from non-asthmatic individuals. NO_x measurement in humid conditions has also not been done exhaustively. These lacunas should be filled in by the future researchers. Table II summarises the major research contributions in trace NO detection.

Ammonia concentration in the exhaled breath of healthy human beings range from 425–1800 ppb with a mean of 960 ppb. Molybdenum oxide and tungsten oxide have exhibited high selectivity towards ammonia. Mutschall et al.[127] reported that reactively sputtered thin film of rhombic MoO_3 can detect ammonia at temperatures of 400 °C−450 °C. Imawan et al.[128] reported that use of Ti overlayers on sputtered MoO_3 thin films can enhance the sensitivity and selectivity towards ammonia while reducing cross-sensitivity towards carbon monoxide, sulphur dioxide and hydrogen. Sunu et al.[129] suggested that ammonia sensing mechanism of MoO_3 involves formation of molybdenum suboxide and nitrides. Gouma et al.[130] was able to detect down to 50 ppb ammonia employing spin coated MoO_3 synthesized by sol-gel route. Jodhani et al.[131] could measure down to 500 ppb ammonia using flame spray synthesized pristine α-MoO_3 Nanosheets. Prasad et al.[132] compared ammonia sensing properties of sol-gel prepared and ion beam deposited MoO_3 thin films. It was revealed that ion beam deposited thin films could detect ammonia down to 3 ppm, whereas the sol-gel deposited thin films could detect down to 8 ppm ammonia. Very recently, Kwak et al.[133] reported to have detected ammonia down to 280 ppt using hydrothermally synthesized α-MoO_3 nanoribbons (MoO_3 NRs). However, most of these tests were conducted at dry atmospheres, whereas exhaled human breath contains almost saturated moisture. Also, the ammonia sensing properties of MoO_3 is given to acid-base interaction, which might be adversely affected at high %RH conditions, thereby affecting the sensitivity and selectivity of the sensor. Gunter et al.[134] fabricated a chemorestive gas sensor based on Si-stabilized α-MoO_3 made by flames and it could sense ammonia down to 400 ppb even at 90% relative humidity. This research is therefore very important and more of future research needs to focus on this problem.

Srivastava et al.[135] reported that WO_3 thick film with a over-coating of Pt catalyzed silica-niobia layer could detect down to 15 ppm ammonia at 450 °C with a response time of less than 30 s.

Table II. Detection of NO using semiconductor metal oxides.

Nanomaterial	Morphology	Lowest concentration of NO detected
WO_3	Villi-like	200 ppb[121]
WO_3	Nanotube	1 ppb[122]
WO_3/Cr_2O_3	NA	18 ppb[123]
ZnO	Hollow sphere	10 ppm NO_2[124]
γ- WO_3	NA	10 ppm[125]
WO_3	Thin film	60 ppm[126]

Jimenez et al.[136] reported that 5%Cr doped WO_3 shows excellent response to 500 ppb ammonia. Earlier, Jimenez et al.[137] reported the ammonia sensing properties of Cu (0.2% and 2%) and V (0.2% and 2%) doped WO_3. Comparing these two reports it seems that Cr doping increases the sensitivity to ammonia more that Cu or V. Zamani et al.[138] reported that chemically prepared mesoporous 2% Cr doped WO_3 deposited on a MEMS platform was capable of detecting 5 ppm ammonia with highest sensitivity observed at 350 °C. Jeevitha et al.[139] prepared porous rGO/WO_3 nanocomposite that could detect ammonia down to 1.14 ppm at room temperature (32 °C−35 °C) and 55% relative humidity. Wu et al.[140] detected ammonia down to 5 ppm with tin monoxide nanoshells with a p-type response of 313%. Zhang et al.[141] prepared ZnO/MoS_2 nanocomposite which comprised of ZnO nanorods and MoS_2 nanosheets. The sensor could detect down to 500 ppb ammonia. Table III summarises the major research contributions in trace ammonia detection.

As already discussed, acetone is considered to be the breath biomarker of diabetes. Amongst all the nano-materials capable of detecting acetone in the form of VOC, semiconductor oxides top the list. The two major oxides showing maximum response to acetone are WO_3 (tungsten oxide) and Fe_2O_3 (iron oxide). Choi et al.[160] reported that Pt functionalized WO_3 hemitube with wall thickness of 60 nm exhibited superior sensitivity to acetone (R_{air}/R_{gas} = 4.11 at 2 ppm) with a detection limit of 120 ppb and 7 month stability. In another paper Choi et al.[161] demonstrated that Pt loaded porous WO_3 nanofiber showed excellent sensitivity to acetone with response of 28.9 [R_{air}/R_{gas}] to 5 ppm acetone vapor. Kim et al.[162] reported the excellent acetone sensitivity (R_{air}/R_{gas} =62 at 1 ppm) of apoferritin encapsulated Pt doped electro-spun meso-porous WO_3. Righettoni et al.[109] reported an ultrasensitive Si doped ε-WO_3 sensor which had a detection limit of 20 ppb and could differentiate between 0.9 ppm and 1.8 ppm acetone vapor even at 90%RH at 400 °C operating temperature. In another literature, Righettoni et al.[108] demonstrated that 10 mol% silica (SiO_2) doped WO_3 can have a detection lower limit of 20 ppb to acetone. In yet another literature Righettoni et al.[163] compared the results of Si doped WO_3 and PTR-MS in detecting acetone in real human breath and appreciable correlation was demonstrated. Recently, Kim et al.[164] reported that apoferritin modified ruthenium oxide quantum dots (Ru_2O) functionalized, electrospun WO_3 nanofibers can effectively detect acetone vapor (R_{air}/R_{gas} =78.61 at 5 ppm) even at 95% RH. Earlier the same group[165] reported that Rh_2O_3-decorated WO_3 nanofibers has a sensing response of R_{air}/R_{gas} = 41.2 at 5 ppm acetone vapor at highly humid conditions (95% RH). Xu et al.[166] reported that electrospun WO_3 based hierarchical structure with mesopores of uniform and controlled sizes and interconnected channels prepared by sacrificial templates of silica and polyvinylpyrrolidone (PVP) can detect sub-ppm (<1 ppm) acetone.

Another very important oxide in trace acetone detection is iron oxide. Sen et al.[167] patented a Pt and antimony oxide (Sb_2O_3) doped γ-iron oxide (γ-Fe_2O_3) composition that could effectively detect down to 1 ppm acetone even in humid conditions. Cheng et al.[168] reported the trace acetone sensing behavior of Eu- doped α-iron oxide nanotubes and nanowires. It was observed through their study that the Eu doped α-Fe_2O_3 nanotube has a superior sensitivity (about 2.7 times) over the nanowires at 100 ppm of acetone. The detection limit was 0.1 ppm with fast response and recovery.

There are other miscellaneous oxides which have shown excellent sensitivity to ppm(v) to ppb(v) acetone vapor. For example, Narjinary et al.[169] showed that a sol-gel derived composite of tin-di-oxide (SnO_2) and multiwalled CNT could efficiently detect acetone down to 1 ppm with sufficiently fast response and recovery time. Chakraborty et al.[170] reported that sol-gel derived bismuth ferrite nanoparticles could detect down to 1 ppm acetone with an appreciable sensitivity of R_{air}/R_{gas} = 1.8 at 350 °C. She also explained the plausible underlying mechanism. Abokifa et al.[171] were able to detect acetone at room temperature using tin dioxide nanocolumns preaped by aerosol-route. The experimental results were validated using density functional theory based theoretical modeling. Priya et al.[172] observed that 2 wt%

Table III. Detection of NH_3 using semiconductor metal oxides.

Nanomaterial	Morphology	Lowest concentration of NH_3 detected
Rhombic MoO_3	Reactively sputtered thin film	25 ppm[127]
MoO_3 with Ti overlayer	Sputtered thin film	50 ppm[128]
Spin coated MoO_3	NA	50 ppb[130]
α-MoO_3	Nanosheets	500 ppb[131]
α-MoO_3	Ion beam deposited	3 ppm[132]
α-MoO_3	Nanoribbons	280 ppt[133]
Si doped α- MoO_3	Needle like morphology	400 ppb[134]
WO_3 thick film with a overcoating of Pt catalyzed silica-niobia layer	NA	15 ppm[135]
5wt% Cr doped WO_3	NA	500 ppm[136]
V and Cu doped WO_3	NA	500 ppm[137]
2wt% Cr doped WO_3	Mesoporous nanoparticle	5 ppm[138]
Pt and Cr-doped WO_3 thin films	Mesoporous nanoparticle	6.2 ppm[142]
rGO/ WO_3 nanocomposite	Porous nanosheets with nano-spherical WO_3	1.14 ppm[139]
SnO_2	nano-shell	5 ppm[140]
ZnO/MoS_2	Self-assembled	500 ppb[141]
Pure and Pt-doped WO_3	Nanoparticle	100 ppm[143]
Pure and Pt loaded WO_3	Mesoporous	50 ppm[144]
WO_3	Nanowire	1500 ppm[145]
Pure & Cr and Pt doped WO_3	Macroporous	6.2 ppm[146]
WO_3	Nanorods	50 ppm[147]
$W_{18}O_{49}$	Nanowire	100 ppb[148]
Polypyrrole -WO_3 composite	Nanofiber	1 ppm[149]
WO_3	Nanofiber	50 ppm[150]
Pure and Cr–WO_3	NA	50 ppm[151]
WO_3	Nanorods	25 ppm[152]
rGO−SnO_2 composite films	NA	25 ppm[153]
bilayer thin film of SnO_2–WO_3	NA	50 ppm[154]
PANI/WO_3 composite	NA	10 ppm[155]
SnO-PANI nanocomposite	NA	100 ppm[156]
rGO/WS_2 heterojunction	NA	10 ppm[157]
Flexible graphene based wearable gas sensor	NA	ppt level[158]
ZnO with functionalized CNT and Graphite	NA	~40 ppm[159]

Au doped electrospun SnO_2 exhibited trace acetone sensing at 250 °C. Also, spray deposited gallium doped SnO_2 has been reported to detect low ppm acetone vapor at 350 °C.[173] 2 wt% Ni doped zinc oxide thin film acetone sensor prepared by spray pyrolysis method was reported by Khalidi et al.[174] Hydrothermally prepared Pt-functionalized nanoporoustitania (TiO_2) was reported to detect acetone in ppm(v) level by Xing et al.[175] Electrospun indium oxide (In_2O_3) nanowire with a controllable Pt core was prepared by Liu et al.[176] and it could detect down to 10 ppb acetone vapor. It had a fast dynamic process, good selectivity and long-term stability. The molecular sieve employed decreases the deleterious effect of moisture to a great extent. The authors claimed that this sensor has the potential of becoming an inexpensive, simple, non-invasive diabetes detector. To develop humidity-independent acetone sensor Yoon et al.[177] decorated hollow In_2O_3 spheres with CeO_2 nanoclusters. It was demonstrated that indium oxide spheres with $\geqslant$11.7 wt% cerium oxide surface loading results into excellent humidity-independent acetone sensing. Jang et al.[178] developed apoferritin modified Pt-functionalized, highly porous SnO_2 by electrospinning method using polyvinylpyrrolidone (PVP) and polystyrene (PS) as sacrificial pore formers. The functional material so developed has excellent sensitivity ($R_{air}/R_{gas} = 192$ at 5 ppm) and lowest detection limit of 10 ppb. Shin et al.[179] developed thin walled, assembled SnO_2 nanofibers with wrinkled layers and elongated channel like pores and voids that enhanced the sensitivity towards acetone with respect to densely packed SnO_2 nanofibers. Also, surface decoration with Pt nanoparticles markedly enhances the sensitivity. The lowest detection limit was reported to be 120 ppb of acetone vapor. Also, Koo et al.[180] reported that Pd doped $ZnO/ZnCo_2O_4$ hollow spheres prepared by metal-organic template method has notable sensitivity and selectivity to trace acetone (69% sensitivity to 5 ppm acetone at 250 °C).

Humidity and ethanol in breath are two major cross-sensitive agents that might hinder the efficacy of a metal oxide acetone vapor sensor from exhaled breath. In many of the abovementioned works the effect of humidity has been nullified or reduced to a great extent by increasing the operating temperature, using a moisture trap, or just by tuning the composition and morphology. However, further developments in this regard are necessary. Ethanol concentration in the breath of a healthy individual is generally much lower than that of acetone. However, for an intoxicated person it ramps up to 100 s of ppm. That can hinder the selective detection of acetone. In this regard acidic oxides, such as tungsten oxide (WO_3) have proven better than the basic oxides. However, more work needs to be done in this field. Table IV summarises the major research contributions in trace acetone detection.

As already mentioned in Table I; hydrogen sulphide (H_2S) is a breath biomarker for halitosis. The major oxides that can detect trace H_2S (<1 ppm range) are copper oxide (CuO), tin dioxide (SnO_2), indium oxide (In_2O_3), zinc oxide (ZnO), titanium oxide (TiO_2) and iron oxide (Fe_2O_3). Steinhauer et al.[201] developed CuO nanowires by on chip thermal oxidation of electroplated Cu and these nanowires owing to their high surface to volume ratio could detect down to 10 ppb H_2S. Vertically aligned CuO nanowire array based sensor prepared by in situ SEM micro-manipulation was employed by Chen et at[202] to detect down to 500 ppb H_2S. CuO nanosheets were developed by Zhang et al.[203] for selective and sensitive detection of trace H_2S down to 2 ppb. It is worth mentioning that this material exhibited strong recovery. Ramgir et al.[204] prepared CuO thin films by oxidation of Cu film deposited by thermal evaporation technique and this material was capable of detecting sub-ppm H_2S. Importantly, at low concentrations of 100–400 ppb the response and recovery were reasonably fast, 60 s and 90 s, respectively. Hierarchical hollow porous sphere of CuO were developed by Qin et al.[205] The sensor showed excellent detection lower limit (2 ppb), response (3 s) and recovery (9 s) time towards H_2S.

About two decades ago, Tamaki et al.[206] reported that a thin film sensor prepared from a composite of CuO-SnO_2 could detect 0.02 ppm H_2S at 300 °C. Similarly, CuO loaded SnO_2 naowires were developed by Giebelhaus et al.[207] for enhancing the sensitivity towards H_2S. The p-n heterojunction formed at the CuO-SnO_2 interface was responsible for the enhanced detection ability of the material. Xue et al.,[208] also hypothesized that the p-n junction developed at the interface of CuO-SnO_2 core/shell structure developed by them, was responsible for the heightened H_2S sensing ability of the sensing material. Similar composite was also developed by Hwang et al.[209] In their work they reported that CuO sensitized SnO_2 nanowire showed 74 times higher sensitivity than SnO_2 nanowire alone at 20 ppm H_2S. The recovery time was short (1–2 s) and the cross-sensitivity to NO_2, CO, ethanol and C_3H_8 were also negligible. Choi et al.[210] had similar findings with CuO decorated SnO_2 hollow spheres. Sb-doped SnO_2 capable of detecting 100 ppb H_2S at room temperature was reported by Ma et al.[211]

CuO decoration is found to be effective for selective H_2S detection also on In_2O_3. Liang et al.[212] reported that CuO loaded In_2O_3 naowires can effectively detect low concentrations, viz. 5 ppm of hydrogen sulphide selectively with respect to NO_2, H_2, CO, NH_3, C_2H_5OH, C_3H_6O, TMA, C_7H_8, and C8H10 at room temperature and 150 °C. The high surface area of the 1-D nano-structure and the abundance of p-n heterojunction formed at the interface of the two oxides have been pointed out as the reasons for such high sensitivity and selectivity.

Hollow spheres of ZnO-CuO prepared by hydrothermal method also revealed high response to 5 ppm H_2S and negligible cross-response to much higher concentrations of C_2H_5OH, C_3H_8, CO and H_2 at 336 °C.[213] In this paper also, Kim et al. pointed out the abundance of p-n heterojunctions formed at the ZnO-CuO interface within the hollow spheres as the plausible sensing mechanism.Wo et al.,[214] reported that Mo-doped ZnO nanowire network sensors displayed excellent sensitivity to 5 ppm H_2S (Ra/Rg = 14.11) with negligible cross-sensitivity to C_2H_5OH, NH_3, HCHO, CO, H_2, *o*-xylene, benzene, toluene, and trimethylamine at the same concentration level. Mo decoration at the surface effectively increases the sensitivity and selectivity to H_2S. A novel cage-like ZnO-MoO_3 composite was developed by hydrothermal method by Yu et al.[215] for detection of trace H_2S down to 500 ppb. MoO_3 itself turns up as a selective and sensitive H_2S sensor. Excellent response to H_2S in air down to 5 ppm was observed by Galstyan et al.[216] using long chains ($\leqslant$30 μm) of ZnO nanobeads prepared by anodic oxidation of sputtered Zn film followed by oxidation. Hydrothermally synthesized ZnO nanorods capable of detecting down to 0.05 ppb H_2S was reported by Wang et al.[217]

Free-standing, semi-transparent, flexible MoO_3 nanopaper was utilized by Li et al. to detect H_2S down to 0.25 ppm.[218] A MoO_3-$Fe_2(MoO_4)_3$ core-shell composite that could detect down to 1 ppm H_2S was developed by Gao et al.[219] Mo doped SnO_2 thick-film developed by Kabcum et al.[220] was capable of detecting down to 0.25 ppm H_2S. SnO_2 yolk-shell nanostructure with uniform Ag surface-loading prepared by Yoon et al.[221] also exhibited excellent sensitivity towards H_2S ($R_a/R_g - 1 = 613.9$, to 5 ppm H_2S). Ag doping worked well with TiO_2 also. Ma et al.[222] discovered that the said nanostructure could detect down to 1 ppm H_2S.

Further, low-temperature Ag-doped α-Fe_2O_3 based H_2S sensor capable of detecting down to 50 ppm H_2S was developed by Wang et al.[223] Tian et al.[224] reported that hierarchical, hollow nano-boxes of Fe_2O_3 were capable of detecting down to 0.25 ppm H_2S with sufficiently fast response and recovery time. Ultrasensitive low-ppm H_2S sensor was prepared by Ma et al.[225] using nano-chains of α-Fe_2O_3. Balouria et al.[226] could detect $\sim$10 ppm H_2S using Au modified Fe_2O_3 thin films.

WO_3 is another potential candidate for detection of traces of H_2S from gas phase. Lonescu et al.[227] prepared a semi-thin film ($\sim$20 μm) of WO_3 quantum dots (5nm diameter) that could detect down to 20 ppb H_2S. Pd functionalized highly porous WO_3 nanofiber was reported to be a potential candidate for the detection hilatosis and lung cancer from breath.[228] Gold incorporated vacuum deposited WO_3 thin film was observed to be detecting 100 ppb H_2S.[229]

Table IV. Detection of acetone using semiconductor metal oxides.

Nanomaterial	Morphology	Lowest concentration of acetone detected
Pt functionalized WO_3	Hemitube	120 ppb[160]
Pt functionalized WO_3	Porous nanofiber	5 ppm[161]
Pt doped WO_3	Mesoporous	1 ppm[162]
Si doped ε- WO_3	NA	20 ppb at 90%RH[109]
Ru_2O functionalized WO_3	Nanofiber	5 ppm at 95%RH[164]
Rh_2O_3-decorated WO_3	Nanofiber	5 ppm at 95%RH[165]
WO_3	Mesoporous	<1 ppm[166]
Pt and Sb_2O_3 doped γ-Fe_2O_3	Spherical nanoparticles	1 ppm[167]
Eu doped α- Fe_2O_3	Nanotubes	100 ppb[168]
SnO_2-MWCNT nanocomposite	Spherical nanoparticles and tubular CNTs	1 ppm[169]
Bismuth Ferrite	Spherical nanoparticles	1 ppm[170]
Au doped SnO_2	Nanofiber	2 ppm[172]
Y doped SnO_2	Prismatic hollow nanofiber	20 ppm[181]
Ga doped SnO_2	Thin film	6000 ppm[173]
Eu doped SnO_2	Nanobelt	100 ppm[182]
Ni doped SnO_2	NA	200 ppm[183]
Co doped SnO_2	Thin film	0.1 ppm[184]
Ni and Ce doped SnO_2	Thin film	100 ppm[185]
rGO doped SnO_2	Nanofiber	5 ppm[186]
SnO_2/Au-doped In_2O_3 heterojunction	Coaxial nanofiber	5 ppm[187]
α- Fe_2O_3/ SnO_2	NA	100 ppm[188]
SnO_2-ZnO	Hetero-nanofiber	100 ppm[189]
SnO_2-TiO_2	NA	200 ppm[190]
SnO_2	Nanowires	20 ppm[191]
SnO_2	Hollow microsphere	50 ppm[192]
SnO_2	Nanotube	20 ppm[193]
SnO_2	Aurelia	10 ppm[194]
SnO_2	Thin film	8 ppm[195]
SnO_2	Nanobelt	5 ppm[196]
Au:$SmFe_{0.9}Zn_{0.1}O_3$	Nanoparticle	0.01 ppm[197]
Ca^{2+} and Au co-doped SnO_2	Nanofiber	10 ppm[198]
Pt functionalized SnO_2	Porous nanotubes	10 ppb[178]
Pt functionalized SnO_2	Thin wall, assembled nanofiber	120 ppb[179]
Ni doped ZnO	Thin film	100 ppm[174]
Pt doped ZnO	Nanoparticle	50 ppm[199]
Nb doped ZnO	Nanoparticle	50 ppm[199]
V doped ZnO	Thin film	100 ppm[200]
Pt-functionalized TiO_2	Nanoporous	200 ppm[175]
In_2O_3 with controllable Pt core	Nanowire	10 ppb[176]
CeO_2 decorated In_2O_3	Hollow spheres of In_2O_3, CeO_2nanocluster	500 ppb[177]

There are multiple other oxides, composites and doped/decorated oxides viz. Co_3O_4,[230] $BaTiO_3$,[231] $YMnO_3$,[232] $CdIn_2O_4$,[233] lanthanum lead iron nickel oxide, iron doped calcium copper titanate[234] etc that are capable of detecting H_2S gas in ppb to 1000 ppm level.

From the above discussion it is clear that the pristine and composited CuO based sensors have the highest potential for detecting hilatosis from breath. Through the discussion of the literatures it is evident that the sensitivity and selectivity can be increased by increasing the surface to volume ratio, increasing the porosity so the target analyte can reach most of the active sites of the functional material and by increasing the number of p-n junctions. So this could be the model for the researchers working in this area. Also, Mo due to its tendency to easily form MoS_2 has been another potential candidate. The major concern in this regard is slow recovery time of most of the sensors that need to improve through future research activities. Also, the quest for novel materials that may stand up to the purpose are in vogue. Table V summarises the major research contributions in trace H_2S detection.

Available literature suggests that amongst all the cancers, lung cancer has the highest possibility of being detected by VOC analysis by semiconductor metal oxides. By far ~30 VOCs have been detected that can collectively be considered as the breath biomarkers of lung cancer. As already discussed aldehydes in exhaled breath are the most potential breath biomarkers of lung cancer. To this end different studies targeted at detecting different such aldehydes (1-nonanol, formaldehyde), long-alkyl-chain molecules, and benzene rings using SnO_2, NiO, Co_3O_4, Cr_2O_3, CuO, and Mn_3O_4 have been attempted. However, detection of lung cancer through exhaled gas analysis is much more difficult than detecting asthma, COPD, diabetes, hilatosis etc because there is no single biomarker for lung cancer. In this regard, scientists are trying to use arrays of non-specific sensors instead of specific sensors in an attempt to detect lung cancer by breath gas analysis. However, in this review we shall concentrate on the specific detection of breath biomarkers and thereby will not discuss any further in this regard.

Major parameters influencing the sensing behaviour.— Morphology, size, and composition of nanomaterials play pivotal roles in determining key sensing parameters, such as, sensitivity, selectivity, and response/recovery time. Materials chemistry can be an effective tool in tailoring the shape, size, and composition of the nanomaterials. Figure 6 shows the basic parameters influencing sensing behavior.

Major parameters affecting sensitivity.—Gas/VOC sensing in semiconductor oxides is a surface phenomenon. Therefore, as surface to volume ratio (S/V) increases with decreasing particle

Table V. Detection of H_2S using semiconductor metal oxides.

Nanomaterial	Morphology	Lowest concentration of H_2S detected
CuO	Nanowire	10 ppb[201]
CuO	Vertically aligned nanowire	500 ppb[202]
CuO	Nanosheet	2 ppb[203]
CuO	Thin film	100 ppb[204]
CuO	Hierarchical hollow porous sphere	2 ppb[205]
CuO-SnO_2	Thin film	20 ppb[206]
Sb doped SnO_2	Nanoribbon	100 ppb[211]
CuO loaded In_2O_3	Nanowire	5 ppm[212]
CuO-ZnO	Hollow sphere	5 ppm[213]
Mo doped ZnO	Nanowire	5 ppm[214]
ZnO-MoO_3	Cage	500 ppb[215]
ZnO	Long chain of nanobeads	5 ppm[216]
ZnO	Nanorod	0.05 ppb[217]
MoO_3	Nanopaper	0.25 ppm[218]
MoO_3- $Fe_2(MoO_4)_3$	Core-shell	1 ppm[219]
Mo doped SnO_2	nanoparticle	0.25 ppm[220]
SnO_2@Ag	Yolk-shell	5 ppm[221]
Ag doped TiO_2	Nanostructure	1 ppm[222]
Ag doped α- Fe_2O_3	Nanostructure	50 ppm[223]
α- Fe_2O_3	Hierarchical hollow nano-box	0.25 ppm[224]
α- Fe_2O_3	Nanochain	ppb level[225]
Au modified α- Fe_2O_3	Thin film	~10 ppm[226]
WO_3	Quantum dot	20 ppb[227]
Pd functionalized WO_3	Porous nanostructure	—[228]
Au incorporated WO_3	Thin film	100 ppb[229]

size, sensitivity also increases. One of the methods of increasing S/V is to decrease the crystallite/particle size. For example, Xu et al.[235] showed that when the particle size of SnO_2 was reduced, the sensitivity towards CO and H_2 increased.

Another method of increasing surface area is by tailoring the particle morphology. 1-D structure, viz. nano-wire and nano-rods have the highest S/V. 2-D structures have relatively lower S/V and 3-D structures have the lowest S/V. Amongst 3-D structures sphere has the lowest S/V. Therefore, recently the thrust is on developing 1-D Nanomaterials. For example, Steinhauer et al.[201] developed CuO nanowires that could detect down to 10 ppb H_2S. In another report Choi et al.[161] showed that Pt loaded porous WO_3 nanofiber could exhibit high sensitivity to 5 ppm acetone with a response of 28.9 [R_{air}/R_{gas}]. Rout et al.[112] clearly showed that WO_3 nanowires have far superior sensitivity with respect to WO_3 nanoplatelets (2-D structure) which again has higher sensitivity than spherical WO_3 nanoparticles, thereby proving the point again that enhanced S/V increases sensitivity.

As much as it is important to have high S/V, it is also of paramount importance that maximum available surface should be exposed to the target gas/VOC. For example, WO_3 based hierarchical structure with uniform mesopores of controlled sizes and interconnected channels were found to detect sub-ppm acetone.[166] Highly porous electrospun SnO_2 was found to have extremely high sensitivity ($R_{air}/R_{gas} = 192$ at 5 ppm) to acetone.[178] Shin et al.[179] clearly showed the advantage of higher porosity by demonstrating that densely packed SnO_2 nanofibers had much inferior sensitivity as compared to assembled SnO_2 nanofibers with wrinkled layers and elongated channel like pores and voids.

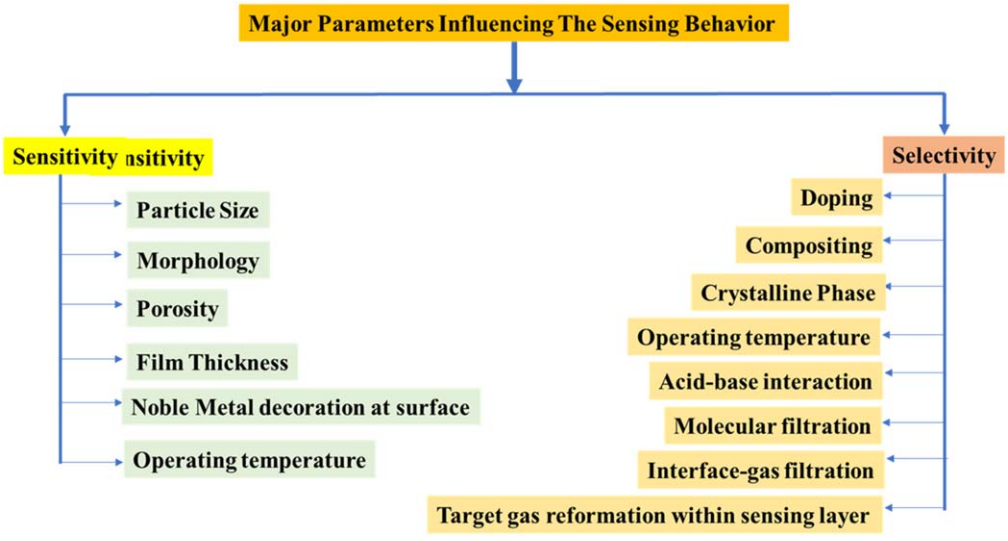

Figure 6. Major parameters affecting sensing behavior.

Thickness of the sensing layer also affects the sensitivity of the sensor. Here also the same logics of S/V and surface area accessible to gas/VOC are applicable. As the sensing layer becomes progressively thinner, at some point of time it becomes thin film. A thin film is a virtually 2-D structure, whereas a thick film is a 3-D structure. Therefore, S/V ratio of thin film is much higher than thick film and hence in thin film sensitivity becomes higher. Also, in a thick film the inner part of the sensor coating is virtually unaccessible to the target gas/VOC. But in a thin film almost all the surface is available to the target gas. Therefore, absorption increases and also sensitivity. There have been multiple reports on thin film chemiresistors and their beneficial effects on sensitivity[126–128,132,142,154,174,184,195,204,206,226,229,200] and these have been discussed in necessary details in the previous part of this section.

Another interesting practice for increasing sensitivity is by decorating the oxide nanoparticles with noble metal nanoparticles. For example, Sen et al.[167] demonstrated that decorating γ-Fe_2O_3 with Pt enhaced the nanomaterial's sensitivity and selectivity towards low ppm acetone. Pt functionalized WO_3 hemitube exhibited enhanced sensitivity to acetone ($R_{air}/R_{gas} = 4.11$ at 2 ppm) with a detection lower limit of 120 ppb.[160] Pd functionalized WO_3 and Au incorporated WO_3 thin film demonstrated enhanced sensitivity towards H_2S.[228,229]

Also, the working temperature should be as optimized. At very low temperatures there are not enough electrons in the conduction band and hence sensitivity will be low. On the other hand, at very high temperatures the desorption kinetics much surpasses the absorption kinetics, thereby reducing the sensitivity. Therefore, optimum operating temperature lies somewhere in between and this needs to be identified in each case. For room temperature sensors the band structure is manipulated such that there are enough electrons in the conduction band even at room temperature, thereby ensuring appreciable sensitivity at room temperature itself.

Major parameters affecting selectivity.—Other than sensitivity, selectivity is another important parameter of a gas sensor. Selectivity can be enhanced by few techniques, viz. doping the sensing material, changing the crystalline phase of the sensor material, and by varying the operating temperature. Humidity is one of the major cross-sensitive agents in case of breath analysis. Tricoli et al.[236] doped SnO_2 with 5% TiO_2 to reduce the cross-sensitivity to humidity and increased the sensitivity to ethanol. Si-stabilized flame-made α-MoO_3 exhibited reduced sensitivity to even 90% humidity.[134] Similarly, Ti overlayer on MoO_3 thin films reduces cross-sensitivity towards carbon monoxide, sulphur dioxide, and hydrogen and increases sensitivity towards ammonia vapor.[128] rGO/WO_3 nanocomposite showed selective sensing towards 1.14 ppm ammonia even at 55% relative humidity.[139] Antimony trioxide (Sb_2O_3) doping in γ-Fe_2O_3 reduced humidity sensitivity with respect to pristine γ-Fe_2O_3.[167] Myriads of other such example can be put forward. In this regard this should be mentioned that inspite of huge amount of research, the effect of doping and compositing on selective sensing of gas/VOCs is still highly empirical and unpredictable. One has to intuitively choose his dopant/ compositing material based on his work experience in the field and detailed knowledge of the prior art. To that end we have included a nearly exhaustive survey of oxides and their dopants/composites for sensitive and selective detection of major breath biomarker gases/VOCs (ref. sub-section "Semiconductor Oxides" and Tables II–V). However, in general it may be mentioned that generally transition metal oxides enhance selectivity and noble metal alloys decrease selectivity. However, noble metal alloys tend to increase selectivity.

It has been noted by some researchers that changing the crystalline phase might enhance selectivity towards a particular gas. For example, ε-WO_3 has an affinity towards trace acetone.[106,108] Similar example is γ-Fe_2O_3 which shows better affinity towards sub-ppm acetone as compared to α-Fe_2O_3.[167] α-MoO_3 exhibited is more selective to ammonia than the other crystalline phases of the same oxide.[133] Again, the choice of crystalline phase of oxide for the selective detection of a particular gas/VOC is done purely based on the knowledge of prior art, experience in the field and by trial and error method.

There is another prominent factor that affcts selectivity, viz. the operating temperature of the sensor. For example, NH_3 selectivity can be improved by selecting the operating temperature of 400 °C to 450 °C in α-MoO_3.[127] Selectivity towards sub-ppm acetone over humidity could also be increased by selecting an operating temperature of 300 °C.[167]

Further there are some other factors affecting selectivity. Cho et al.[117] reported that acid-base interaction between the acidic oxide of α-MoO_3 and basic vapor of triethylamine is responsible for ultrasensitive (detection limit down to 45 ppb) and ultraselective (in presence of multiple other gases, such as, C_2H_5OH, CO, CH_4, C_3H_8, H_2, and NO_2) detection of triethyl amine. Molecular filter may also increase selectivity. Sahm[120] et al. reported that the Pd doped and undoped SnO_2 sensor showed better selectivity towards methane (230 ppm) in presence of a molecular filter of Pd doped Al_2O_3. There are also some less practiced techniques described earlier in this section.[118–120]

Semiconductor chalcogenides and C based semiconducting materials.—Recently, these materials have spurred interest in researchers owing to their potential to detect breath biomarkers. However, the gas sensing behavior of these materials has not been studied that well until now. By far disilicides and diselenides of molybdenum and tungsten has been studied as gas sensors. The most probable sensing mechanism is the charge transfer reaction between the target analytes and the material. Although many literatures suggest that these materials exhibit p-type gas sensing behavior, it still remains elusive whether these materials are n-type or p-type semiconductors. However, these materials can detect both polar (ammonia and NO_x) and non-polar (CO and methane) gases.[237–239] This is an advantage as compared to the CNT and rGO based gas sensors. These materials can not be used above 300 °C, for oxidative degradation starts near about that temperature. Nevertheless, these materials most certainly revealed themselves to be potential candidates for breath analysis sensors.

Carbon nanotube (CNT) has attracted huge attention since its discovery owing to its excellent physical and chemical properties, such as high surface to volume ratio and high surface activity.[240,241] CNT interacts with gas molecules at room temperature by charge transfer between gas/VOC molecules adsorbed at the surface and the CNT itself and acts like a p-type semiconductor.[242] The sensing properties of CNT depends on chirality, impurities, and defects in the structure.[243,244] It shows negligible interactions with the major breath gases, viz. nitrogen, oxygen, and water vapor. But it interacts well with other breath gases such as ammonia and NO_x. Therefore, it seems to have great potential for breath analysis.

Graphene is another exotic functional material which might become useful in selective detection of breath biomarkers. Graphene has high surface to volume ratio and behaves like a p-type semiconductor. However, direct preparation of graphene is costly and hence in many cases it is prepared from graphene oxide by reduction (reduced graphene oxide, rGO). Pristine rGO can detect ammonia and NO_x[245–247] while rGO with functionally modified surface is known to detect other breath biomarkers, viz. acetone.[248]

CNTs, Graphene and semiconductor chalcogenides are potential candidates for the detection of ammonia and NO at lower temperatures than that of the oxides. Some of the important materials in this regard are MoS_2,[237] electrokinetically fabricated CNT,[249] spin coated monolayer film of grapheme on interdigital electrodes,[250] cellulose derivative assisted dispersion of single-walled CNT (SWCNT),[251] ZnO functionalized graphene and MWCNT,[159] reverse-biased graphene/silicon heterojunction Schottky diode,[252] self-assembled r-GO nanosheets formed on high aspect ratio SU-8 micro-pillar arrays,[253] etc. Ng et al.[254] developed a nanocomposite gel comprised of uniform porous structure and a mixture of 3-D graphene material and an ionic liquid (1-butyl-3-methylimidazolium

hexafluorophosphate). The major advantage of using graphene, r-GO, SW- and MW-CNTs, and semiconductor chalcogenides lie in their low operating temperature and flexible structure.

Electrochemical sensors.—Use of electrochemical sensors for breath analysis to detect disease is a relatively novel field of research with much fewer reports with respect to that of semiconductor sensors. However, due to well-understood operating principle, high accuracy, low detection limits, wide-range of detection, biocompatibility, miniaturizability, low power consumption, and low cost the electrochemical senors are gaining popularity amongst breath researchers.The few drawbacks of these sensors are long response time and inability to detect long chain VOCs.The enzyme based electrochemical sensors are highly selective, however, the non-enzymatic sensors suffer from cross-sentivities from breath moisture and other competing VOCs/gases. The electrochemical cells that use aqueous electrolyte have to use gas permeable, hydrophobic membrane that allows the inward diffusion of gas but suppresses the outflow of water. Thus, the process becomes diffusion controlled and response time becomes very long. Multiple techniques have been adopted to solve this problem but the best solution is "fuel cell" technology that uses solid-electrolyte.

The most commonly detectable VOCs/gases by electrochemical technique are CO, NO, hydrogen peroxide, low chain-length aldehydes, and ethanol vapor. However, ethanol is not a breath biomarker for any disease or health condition. However, CO, NO and also hydrogen peroxide concentration in exhaled breath increase in case of airway inflammation, asthma, COPD, oxidative stress, lung cancer, and other such respiratory diseases. Therefore, the electrochemical detection of these biomarkers will be mostly discussed with one or two examples of breath alcohol analysis by electrochemical technique. The sole reason for including breath alcohol analysis is the fact that it is important for drunken driving testing. Already, BACtrack, a US based company has made fortunes making "fuel cell" based portable, commercial breath alcohol analyzers. There are very few reports on electrochemical detection of acetone in vapor phase for non-invasive detection of diabetes and ketosis. Those will also be discussed. Also, portable halimeters exploiting electrochemical methods are available commercially. A halimeter measures VSCs (Volatile Sulphur compounds, viz. hydrogen sulfide, methylmercaptan, other thiols, and dimethyl sulfide) for the detection of halitosis. The detection limits are as low as 5 ppb with response time of 1 s.[255] Further, there are electrochemical sensors that can detect ammonia from gas phase, but those were developed for air quality monitoring applications. Their specifications do not match well with the requirements of breath ammonia detection. Therefore, those discussions have been avoided in this review. However, interested readers may refer to the excellent review by R. Baron.[256]

A standard electrochemical sensor consists of a working electrode, a reference electrode, and a counter electrode. The gas/VOC passes through a permeable membrane and gets oxidized or reduced on the working electrode surface. The transfer of electrons that takes place as a result of the redox reaction flows form the working electrode through an external circuit and thereby generates the signal considered as the response of the electrochemical sensor. The purpose of the reference electrode is to indicate the potential of the electrolyte. The external circuit maintains the voltage across the working electrode and the reference electrode and also measures, amplifies, and processes the signal generated at the working electrode. Equal and opposite reaction occurs at the counter electrode, i.e., if oxidation takes place at the working electrode, reduction takes place at the counter electrode.

As has been already mentioned CO can be considered as a biomarker for hemolytic disease. However, fire fighters come across huge concentrations of CO while extinguishing big fires. Therefore, the content of carboxyhemoglobin increases in their blood which can lead to fatal conditions. During this period the exhaled breath CO content also increases. It nessicitates the development of a portable device using which the fire-fighter can measure his own breath CO content after extinguishing a fire and if the CO level in his breath is above the danger limit, he can seek immediate medical attention avoiding any casualty. In 1976, Stewart et al.[257] developed such an electrochemical device that can complete the measurement within 11–12 min in the real field.

Thereafter in 1994, Vreman et al.[258] reported the development of a device based on an amperometric electrochemical sensor for the detection of trace CO from exhaled breath. Reportedly, CO can be a biomarker for hemolytic disease. Platinum black coated Teflon was used as the working electrode. The performance of this device was found to be comparable with that of GC. In 2004, Hemmingsson et al.[259] reported the development of an amperomatric electrochchemical sensor based hand-held device for the real-time detection of NO from exhaled breath. The device was capable of detecting down to 3 ppb NO with a fast response time of 15 s only. The performance of this device was comparable with that of the FeNO testing considered as the gold standard for trace NO detection. Mondal et al.[260] developed a potentiometric electrochemical sensor for the detection of trace NO_x from exhaled breath. They used a 2-electrode system, whereby the working electrode was fabricated by coating Pt wire with tungsten oxide (WO_3) and the reference/counter electrode was fabricated by coating Pt loaded zeolite on Pt wire. Yttria stabilized zirconia (YSZ) was used as the solid electrolyte. Instead of a single sensor, an array of 20 sensors were used to increase the detection limit down to 5 ppb. The calibration of NO_x with EMF was linear enough. Obermeier et al.[261] developed an electrochemical system to simultaneously detect CO, NO, and C_1-C_{10} aldehydes. The electrochemical sensors were amperometric in nature and were all procured from IT Dr Gambert GmbH Wismar, Germany (Dr Kerstin Wex). Both in vitro and in vivo measurements were conducted. The sensors were more sensitive than some chemoresistive sensors but lacked in selectivity. Hydrogen peroxide is known as a biomarker for oxidative stress. In patients with COPD, hydrogen peroxide content in exhaled breath increases. Therefore, monitoring of hydrogen peroxide in exhaled breath can reduce frequent hospitalization and exacerbation of the condition of the affected patient. To this end Wiedemair et al.[262] has developed a chip-integrated, amperometric, electrochemical sensor for the detection of trace hydrogen peroxide in exhaled breath. The working electrode was made of layers of Pt/Ta where Ta was used as the adhesion promoter with the substarte. The counter electrode was made of layers of Ag/Pd/Ti, where Ag is the electrode, Ti was the adhesion promoter and Pd acted as the diffusion barrier between Ti and Ag. The reference electrode was that of Ag/AgCl. Hydrogen peroxide was detected in both liquid phase and gaseous phase. However, in this review we are discussing about direct breath analysis in gaseous phase. For the gas phase measurement of hydrogen peroxide electrolyte with agarose gel dissolved in it was solidified on the electrodes. It was observed that with increasing concentration of hydrogen peroxide in the gaseous phase the current signal increases and the detection limit was estimated to approximately 42 ppb. 2-Butanone is known to be a biomarker for gastric cancer and can be detected in breath condensate.

Zhang et al.[263] reported the fabrication of an amperometric sensor for the detection of 2-butanone. They used an Au/Ag nanoparticle decorated MWCNT loaded glassy carbon electrode as the the working one, a standard platinum wire as the counter electrode and a calomel electrode as the reference electrode. An aqueous solution of KCl was used as the electrolyte to which 2-butanone was dissolved and CV (cyclic voltammetry) study was conducted. The sensor showed high electrocatalytic activity to butanone and there was a linear relationship between the anodic peak current and the concentrations of 2-butanone in the range of 0.01% to 0.075%. Nitrite content in breath condensate was measured by Gholizadeh et al.[264] for point-of-care detection of chronic respiratory conditions such as, asthma and COPD. The primary source of this nitrite being NO in exhaled breath. As already

discussed, the concentration of NO in exhaled breath increases in respiratory inflammatory diseases, therefore, nitrite content should also increase in breath condensate. rGO coated gold electrode was used as the working electrode, Pt and Ag/AgCl were used as counter and reference electrodes, respectively. The sensitivity of the sensor was determined to be 0.21 μA μM^{-1} cm^{-2} in the range of 20 to 100 μM and 0.1 μA μM^{-1} cm^{-2} in the range of 100 to 1000 μM. The lowest detection limit was 830 nM. The results were comparable to the chemiluminescent devices. Mitsubayashi et al.[265] reported that they developed bioelectronic sniffer devices for detection of alcohol (1–100 ppm) and acetaldehyde (0.11–10 ppm) in exhaled breath using enzyme based electrochemical sensors. The alcohol sensor had a carbon electrode and an Ag/AgCl electrode and the enzyme used was alcohol oxidase. The acetaldehyde sensor had two Pt electrodes and the enzyme was aldehyde dehydrogenase. In both cases the change in current due to redox reaction at the working electrode was measured. Breath analysis of aldehyde is important for cancer detection, whereas detection of alcohol from exhaled breath is important for onsite detection of drunken driving.

Recently, Kawahara et al.[266] developed a chronoamperometric, chromatography paper based, enzymatic electrochemical sensor for the detection of ethanol vapor in the breath of an intoxicated person. The beauty of this device lied in the fact that the paper sensor was disposable, low cost, the power source was only a smart phone, and cost-effective graphite pencil was used to fabricate working and counter electrodes. In principle this technique can be used for any breath volatile/gas. Due to the enzymatic approach the selectivity of the sensor is unquestionable.

In the last few years, there have been two excellent reports on breath analysis by electrochemical methods for tuberculosis detection by D. Bhattacharya and Y R Smith. In 2016, Smith et al. reported[267] the detection of four tuberculosis (TB) biomarkers (VOBs), viz. methyl phenylacetate, methyl p-anisate, methyl nicotinate, and o-phenyl anisole by electrochemical methods. Coblat functionalized titania nanotube array (TNA) produced by an incipient wetness method and insitu anodic oxidation method were used as functional materials. The insitu cobalt functionalized TNA (iCo-TNA) showed better response and selectivity to the TB biomarkers with concentrations ranging from 275∼360 ppm. Later in 2016, Bhattacharya et al.[268] reported on the development of an electrochemical sensor for the detection of the same four VOBs of TB using a titania nanotube array (TNA) functionalized by Co by an incipient wetting impregnation (IWI) method. Here also, a two electrode amperometric sensing method was applied where the cobalt functionalized TNA was used as the working electrode. The sensors were able to detect low concentrations of the target analytes down to ∼18 ppb. The enhanced sensitivity is attributed to the width of depletion layer that was comparable to half of the thickness of the TNA. As earlier the maximum sensitivity to methyl p-anisate was observed. The selectivity of the sensor to the TB biomarkers was also appreciable. The sensing platform is claimed to be robust, and inexpensive.

As already discussed, acetone is the breath biomarker of diabetes. Recently, some works related to electrochemical detection of trace acetone from exhaled breath has come forward. Martinez et al.[269] reported a PANI/Cellulose/WO_3 based electrochemical sensor that is capable of detecting trace acetone in room temperature. The detection limit of the sensor was reported to be 10 ppm acetone in air. In another report Sorocki et al.[270] reported on a prototype, portable breath analyzer for exhaled acetone detection, the target application being point of care detection of type-1 diabetes. In their report there were no discussion on the functional material.

In brief, this is the current status of breath analysis by electrochemical methods. There are few other reports where electrochemical detectors are used in combination with analytical techniques, such as GC. These detectors can not be directly considered as sensors and are therefore left out of discussion in this review.

Other potential nanomaterials.—Scientists across the globe are constantly investing time, money, and tireless effort in design and development of new materials and techniques of detecting exhaled breath VOCs for the purpose of disease detection. Madasamy et al.[271] developed copper zinc superoxide dismutase (Cu, ZnSOD) that was immobilized on the carbon nanotubes in the polypyrrole modified platinum electrode and this was used as the NO biosensor. Poly (ethylene imine) coated carbon nanotube field effect transistor (NTFET) developed by Kuzmych et al.[272] The conductivity of the FET changed proportionally to the concentration of NO it was exposed to. Kao et al.[273] could detect down to 0.4 ppm acetone using an ultrathin (10nm) InN-FET. de Lacy et al.[274] developed a ppm/ppb level sensor for acetone, acetaldehyde, pentane and ethanol. The sensor was comprised of ultra violet light emitting diode activated zinc oxide nanoparticles that showed reversible resistance change when exposed to the said target VOCs. Gu et al.[275] fabricated Polyaniline/polystyrene single-nanowire based optical devices that were capable of detecting ammonia in ppm level.

Yebo et al.[276] demonstrated reversible ammonia sensing with ammonia-specific acidic nano-porous aluminosilicate film functionalized silicon-on-insulator optical micro-ring resonators. The detection limit was down to 5 ppm. Peng et al.[277] developed a random network of SWCNTs on an oxidized silicon wafer. This was further coated with 11 different non-polymeric organic materials (e.g. Dioctyl phthalate plasticizer, propyl gallate, authracene etc) to develop an array of 11 sensors for differentiating individuals with lung cancer from healthy individuals. Peled et al.[278] used gold nanoparticles coated with 16 different non-polymeric organic materials (e.g. hexanethiol, 2-ethylhexanethiol, 3-methyl-1-butanethiol, octadecylamine, decanethiol etc.) to make an array of 16 non-specific sensors that could effectively differentiate between benign vs malignant pulmonary nodules, between adeno- and squamous-cell carcinomas, and between early stage and advanced stage of lung cancer disease. 72 patients were involved in the study.

Peng et al.[279] conducted a similar study with 177 volunteers in the age group of 20–75 years. Here the gold nanoparticles were functionalized by Dodecanethiol, 4-methoxy-toluenethiol, hexanethiol, 11-mercapto-1-undecanol, decanethiol, octadecanethiol etc (14 non-polymeric organic materials) to develop an array of 14 sensors that was used to detect different cancers, viz. lung, breast, colorectal, and prostate. Hakim et al.[280] diagnosed head and neck cancer from exhaled breath using an array of five sensors made of gold nanoparticles capped by tert-dodecanethiol, hexanethiol, 2-mercaptobenzoazole, 1-butanethiol, and 3-methyl-1-butanethiol ligands. In another work, Broza et al.[281] fabricated an array of 6 sensor prepared by coating organic ligands (11-mercaptoundecanol, oleylamine, dibutyl disulphide, decanethiol etc) on spherical gold nanoparticles and cubic platinum nanoparticles.

Chapman et al.[282] used a carbon polymer array (CPA) to differentiate patients of malignant mesothelioma from patients of asbestos-related disease and healthy individuals with an accuracy of 88%. Dragonieri et al.[283] used a similar kind of electronic nose to differentiate between malignant pleural mesothelioma and controlled healthy individuals. In another study, the author and his team fabricated an e-nose that could discriminate between non-small cell lung cancer and COPD.[284] Organic material coated carbon black and pristine carbon black were used as the functional materials for the sensors of the array. Xu et al.[285] diagnosed gastric cancer from benign gastric conditions using a nanomaterial-based sensor array containing 14 sensors. The sensors are composed of organic, non-polymer material (PAH5, PAH6, 2-ethylhehanethiol, tert-dodecanethiol etc) capped SWCNT and spherical gold nanoparticles. Timms et al.[286] used carbon black to detect gastro-esophageal reflux disease from exhaled breath. Lonescu et al.[287] detected multiple sclerosis from exhaled breath using bilayers of polycyclic aromatic hydrocarbons (PAH1, PAH2, PAH6, PAH7) on SWCNT.

Tisch et al.[288] reported that Alzheimer's and Parkinson's disease can plausibly be detected from exhaled breath using SWCNT and spherical nanoparticles capped by 2-mercaptobenzoxazole, 3-mercaptopropionate, β-cyclodextrin etc. Shuster et al.[289] classified breast cancer precursors through exhaled breath analysis. The e-nose used consisted of an array of sensors comprised of organic non-polymer (benzyl mercaptan, calixarene, octadecylamine etc) coated cubic platinum nanoparticles. Lazar et al.[290] detected asthma from human exhaled breath using an array of 32 carbon black polymer sensors. Carbon black polymers were also employed by Fens et al.,[291] Chapman et al.,[292] and Biller et al.[293] for the detection of pulmonary embolism, obstructive sleep apnea, and airway inflammation, respectively.

Jalal[294] et al. reported to have developed a miniaturized fuel cell sensor based battery operated, wearable device that could detect the concentration of isoflurane (volatile anasthetic). The device is supposed to find application in safe transport of critically ill patients in austere condions in unmanned drones. The electrodes were made of nickel-clad stainless steel and the solid electrolyte was poly-tetra-fluro-ethylene (PTFE) reinforced Nafion424. Ozhikandathi[295] developed a novel ninhydrin-PDMS composite to detect trace ammonia down to 2 ppm. The optical absorption property of the said composite changes when it is exposed to ammonia and that is the working principle of this sensor. Chung et al.[296] repored on a comparison of electrophoretically deposited (EPD) and drop coated hydrothermally synthesized NiO of multiple morphologies on a substrate. The EPD-NiO showed better sensitivity with respect to drop-coated NiO towards ethanol vapor for all morphologies. Ozdemir et al.[297] compared the NO sensitivities of naked porous silicon (PS) and SnO_2 modified PS. It was reported that SnO_2 decorated PS showed much better (10 times higher) response than naked PS at 1 ppm NO exposure. Detection of asthma from exhaled breath was put forward as a plausible application of this sensor.

Therefore, it is clear that non-specific sensor arrays can effectively detect diseases that are difficult to be detected by specific sensors. The general strategy of making such sensors would be to coat functional organic non-polymeric materials on nanoparticles of noble materials (e.g. Au, Pt etc), SWCNT or carbon black. Additionally some fantastic nanomaterials in the field of electrochemical gas sensors are coming up. This opens up new avenues towards the detection of diseases from exhaled breath analysis.

Other techniques.—Alongside the techniques discussed above there are few more techniques that have come in vogue in recent times. Although the focus of this review is not on these techniques, still we will discuss some of these techniques in brief for completeness and to enhance the appeal of this review to a broader readership.

Nanomaterial based field effect transistor (FET).—These materials have advantages over the existing semiconductor gas sensors in regards, such as extreme miniaturizable features, low-power consumption and appreciable control over the sensor signals by controlling the source-gate potential. Shehada et al.[298] used modified Silicon nanowire FETs to detect gastric cancer. Kao et al.[299] used an ultrathin InN FET to detect sub-ppm acetone.

Colorimetric sensors.—As evident from the name colorimetric sensors change color in presence of the target VOCs and the degree of change in color should be related with the concentration of the VOC. Mazonne et al.[300,301] showed that various types of lung cancers can be detected using an array of colorimetric sensors with reasonably good accuracy (for e.g. 81.1%). Alagirisamy et al.[302] used an iodine solution and starch to detect down to 0.05 $\mu g\, l^{-1}$ hydrogen sulphide. The authors demonstrated good correlation between the volatile sulfur compounds (VSC) detected by the developed sensor and halimeter. This study was important for the detection of breath malodor and halitosis from exhaled breath.

Piezoelectric sensor.—It works in conjunction with a quartz crystal microbalance (QCM). The oscillation frequency of QCM changes when it absorbs VOCs and a piezoelectric sensor measures that change. The surface absorption of gases on QCM can be controlled by coating it with various polymers, metal oxides, nanomaterials etc. Lung cancer, COPD, Asthma, and Halitosis was reported to be detected from breath samples by metalloporphyrin-based QMB sensors[303–307] by D'Amico et al., Natale et al., Incalzi et al, Montuschi et al., and Pennazza et al.

Surface acoustic wave (SAW) sensor.—This is a class of sensor based on microelectromechanical systems (MEMS). It converts an input electrical signal into a surface acoustic wave, i.e. a mechanical wave. Unlike the electrical signal the mechanical wave can be easily influenced by the physical phenomena. The modulated SAW is then again converted into an electrical signal that is received at the output end. The changes in amplitude, phase, frequency, or time-delay between the input and output signal can be used to measure any physical phenomenon that might have affected the wave. SAW sensors are coated with various polymers to detect different breath biomarkers and hence various diseases from the exhaled breath. For example, SAW sensors have been used to detect lung diseases,[308] pulmonary tuberculosis[309] etc.

Optical fiber based sensors.—In recent times, Optical fiber based gas sensors have come up in such a big way that a separate review can be written only on this subject. However, here we will merely scratch the surface of what it is. A small part of the cladding is removed and coated with polymer, chemical dye, oxides etc in the form of thin films and when this layer absorbs VOCs, that triggers a change in the refractive index or other transmission properties. Although, different VOCs have been detected using these sorts of sensors, there is by far no report of real exhaled breath analysis using such sensors.

Laser photoacoustic spectroscopy (LPAS).—Carbon dioxide laser is used for this purpose. The laser excites sample gas inside a photoacoustic cell. The photoacoustic signals are proportional to the trace gas concentration. The LPAS has been reported to have been capable of detecting down to 0.2 ppb of ethylene in nitrogen at 1 atm pressure.[310]

Chemiluminescence analyzer.—Chemiluminescence is the standard technique of measuring NO. These sensors are very sensitive and can detect down to ppb-level. It can therefore be used for the detection of asthma from exhaled breath. However, the system is bulky, costly and suffers from drift that needs to be corrected at least once in a year. This limits its use for home monitoring.

Assessment of Exposure to VOCs

Occupational and non-occupational exposure.—Before 2000, employees in petroleum-related industries were considered to be at risk due to potentially hazardous VOCs. Now few other occupations are also in that list, viz. traffic policeman, service station attendants, parking garage attendants, and road side/ underground storekeepers.[311] Benzene, a group I carcinogen, is used as a common solvent in production of petrochemical and pharmaceutical goods, pesticides, synthetic dies etc. Therefore, people working there fall victims to the carcinogenic effects of benzene. It has been established that exhaled breath analysis can be used to differentiate biological benzene levels in healthy individuals from the occupationally exposed individuals 16 h after the end of their working shift.[312] However, smokers have higher benzene levels in breath than normal individuals and hence proper measures should be taken for accurate measurements of occupational benzene levels in their breaths. Some other major aromatic compounds related to occupational exposure are, toluene, xylene and ethylbenzene. Toluene and xylene are found in excess in exhaled breath of house and car painters, varnish workers. Excess of Ethylbenzene and

xylene are found in the exhaled breath of dry cleaners. BTEX (Benzene, toluene, ethylbenzene and xylene) analysis of exhaled breath can be used as a measure of occupational VOC hazard. Other such VOCs are trimethylbenzene, naphthalene, tetrachloroethane, isoflurane etc.

Asbestos is another occupational peril. Although, Asbestos is not a VOC, airborne fine asbestos fibers easily get to the lower portion of lungs with inhaled breath and cause potentially fatal diseases. People working is asbestos mining, processing of asbestos mineral, construction works, mechanics of vehicles, insulation workers in the heating trade, sheet metal workers, plumbers, fitters, cement and custodial workers etc are at risk of falling prey to asbestosis (a fibrotic disease), MPM (Malignant Pleural Mesothelioma, caused by change in the pleural lining), and lung cancer. Biomarkers such as NO, 8-isoprostane, leukotriene B4, α-Pinene (asbestosis) and cyclohexane (MPM) have been identified as breath biomarkers. By far there is no blood test for early detection of MPM. Therefore, breath analysis may have massive impact in the early detection of asbestos related diseases.

Rapid industrialization, increased traffic volumes, increased use of pesticides and synthetic materials etc have elevated the air pollution level to an unforeseen level. Therefore, non-occupational exposure to different VOCs are posing major threats to human health. Most of such VOCs are easily carried to the lungs through inhaled breath and readily absorbed in blood. Therefore, their presence in exhaled breath also increases. NO, SO_x, ammonia, alkanes, halogenated compounds, ketones, aromatic hydrocarbons, terpenes, various alcohols, toluene, xylene etc are some of the major pollutants causing health hazards. As already discussed in previous sections, various studies are going on to detect such volatiles from exhaled breath.

Parameters Affecting VOCs Levels

Other than endogenous processes there are multiple other parameters that affect the VOC levels measured in the exhaled breath.

Exogenous origin.—As discussed in the previous section VOCs such as, NO, NH_3, benzene etc could be of both exogenous and endogenous origin. These could be inhaled or absorbed through skin. Therefore, the concentration of such VOCs in exhaled breath does not necessarily reflect the health conditions. Also, search for new biomarkers are in vogue. Many of the exhaled VOCs are absolutely exogenous in origin. It is therefore important to differentiate between exogenous and endogenous VOCs, so that an exogenous VOC does not wrongly get identified as a biomarker. Background VOC is an issue. It is generally considered that when inhaled concentrations of compounds are greater than 5% of the exhaled concentrations, exhaled breath concentrations can not be correlated to blood VOC concentrations with confidence.

Mouth vs nose exhaled breath.—Exhaled breath analysis is mostly focused on mouth exhaled breath. However, other than VOCs of systemic origin, mouth exhaled breath contains VOCs originating from the airway, from oral cavity and gut by bacterial action, from mucus and saliva. This makes disease detection and health monitoring from exhaled breath difficult. Wang et al.[313] compared exhaled breath from mouth, nose and air in mouth cavity. It was observed that acetone and isoprene are absolutely systemic in origin. Other VOCs, viz. ammonia, hydrogen sulphide, and ethanol are mostly mouth-generated. Methanol, propanol and other VOCs have partly systemic origins. Although concentration of VOCs exhaled from nose have lower concentrations than those in breath, but it obviates the confounding factors present in the mouth exhaled breath. Therefore, nose exhaled breath analysis might be more desirable.

Alveolar breath vs dead space air.—The exhaled breath is a combination of dead space air and alveolar air. Dead space air is defined as the volume of air that acts as a conducting path and alveolar air exchanges VOCs with blood. and VOCs in alveolar breath is supposed to be in equilibrium with the VOCs in blood. It is therefore desirable to measure the alveolar breath. The last fraction of exhaled breath, known as the end tidal breath is close in composition with the alveolar breath.

Dilution of highly water soluble VOCs.—Measurement of less soluble VOCs from exhaled breath is easier. However, for highly soluble VOCs, such as acetone and isoprene such measurement becomes difficult as an anatomic dead-space cannot be defined for such compounds. Most of the exchange of such VOCs occurs at the airway rather than at the alveoli. During inspiration soluble gases are absorbed by the inhaled air in the airway. When it reaches the alveoli, the air is already saturated in soluble gases and no more exchange occurs. During expiration a part of the solubilised gas is re-dissolved in the mucus layer coating the airway. Thus, on the way up the respiratory tract the soluble gases get diluted. Also, an increased blood flow reduces the soluble gas concentration in exhaled breath. It is therefore suggested that holding the breath for 10 s before exhalation may result in more accurate results in exhaled breath analysis.

Influence of age, gender, food and pregnancy.—Isoprene is much less in the breath of children as compared to the adults. At puberty the isoprene concentration is elevated.[314,315] Also, several studies suggest that isoprene concentration in males is more than the females.[316] Further, there are reports of increasing ammonia concentration with age.[22] Clearly, age and gender influence the VOC content in exhaled breath.

It is well-known that intoxication increases exhaled breath ethanol concentration. Also, intake of garlic, onion, mint, banana, coffee, orange, flavoured ice-cream etc are known to change the exhaled breath composition.

Pregnancy in women affects their exhaled breath composition, however no concrete relationship has yet been found.

Influence of storage conditions.—Direct analysis is preferable over storage of breath samples. However, not all breath analysis techniques support direct analysis. Storage should be done with utmost care in order to avoid loss of breath components due to diffusion, background emission of pollutants, VOC influx from the storage container, degradation of the sample by reaction of sample container with the breath VOCs etc. Currently, the most popular way of storing breath is in Tedlar bags. Other materials are Flexfoil bags, Nalophan bags, micropacked sorbent traps, glass vials (SPME), metal canisters etc.

Challenges

Detection of disease and monitoring of health through blood analysis are invasive and painful processes. In the recent past exhaled breath analysis has emerged as a better alternative, mostly because of its non-invasive nature. However, the method is fraught with multiple challenges.

- GC-MS, PTR-MS and SIFT-MS are by far the most accurate techniques for breath analysis. But, these instruments are costly, cumbersome and need trained person for handling, data analysis and data interpretation. These instruments are not like any household devices and can only be available in hospitals and diagnostic clinics. This impedes the use of these instruments as breath analysers on a day to day basis at our homes.One of the major goals of breath analysis is early detection of disease by regular health monitoring and for that to be possible the device used must be financially affordable for common man, easy to use even for a layman and hand held.
- Not all the breath analysis techniques can make use of direct exhaled breath. Breath collection and storage therefore, becomes a

major issue. Collected breath that was stored for a long time often tends to degrade changing their original composition. Also, researchers are still not sure whether nose-exhaled or mouth-exhaled breath should be used for analysis. Even there are disputes regarding testing single and multiple breath. Now a days it is suggested that dead space air should not be considered for analysis, only end-tidal breath should be used. However, for highly water-soluble breath biomarkers, viz. acetone and isoprene there is no anatomic dead space that can be defined. Also, most of the sensor responses are dependent on the exhaled-breath flow-rate onto the sensor head. In direct analysis, patients directly blow on to the sensor head. However, different patients would blow at different flow-speeds, therefore making the measurement complicated. Also, exhaled breath concentration of different gases varies significantly with age, gender, weight, food habits, life style, pregnancy etc. Also, not all the exhaled breath components are endogenous, rather most are exogenous in origin. Many of the endogenous gases are not even systemic in origin. Therefore, locality becomes another confounding factor.

- Semiconductor oxide sensors are cost-effective, rugged, easy-to-use, and handy. They are capable of detecting different breath biomarkers at ppm, ppb or even ppt levels. However, these sensors, in most cases, lack sufficient specificity. Another major problem with these sensors is that they are mostly sensitive to humidity. Human breath contains almost saturated moisture which acts as a major cross-sensitive agent impeding the response of the sensor to target analyte. Presently thick film semiconductor oxide sensors are available in the market. Thick film sensors suffer from lower sensitivity, and high power consumption. Further, their relatively bigger sizes do not allow the integration of multiple such sensors in the form of a sensor array in a single device of reasonably small size to do away with the specificity problem. MEMS based sensor arrays can address the problem of size and power to some extent however, they have other problems. Microsystems generally use moisture traps, which along with moisture adsorbs analyte gases too. Humidity dependence of gas adsorption can significantly reduce the reliability and reproducibility of the preconcentrator. Also, preconcentration requires longer time; thereby making real-time analysis difficult. Further, the small volume of preconcentrator materials present in such microsystem might not be sufficient for detection of trace gases. Also, selective and reversible preconcentration remain challenges.
- Graphene and CNT based materials, FET, Laser, SAW, colorimetry and optical fibre-based sensors are emerging as novel materials and techniques, however, these are far form commercialization.
- In recent times electrochemical sensors have drawn attention of breath researchers owing to well-understood operating principle, high accuracy, low detection limits, wide-range of detection, biocompatibility, miniaturizability, low power consumption, and low cost. However, the technique is not without a few drawbacks, viz. long response time and inability to detect long chain VOCs.
- Specific sensors for the detection of diseases from exhaled breath is limited to a small number of diseases, such as, diabetes, COPD etc which can be detected using a single biomarker. In most of the diseases, especially different cancers, concentrations of multiple breath gases change simultaneously. This is a difficult problem to be handled using specific sensors. Also, use of specific sensors demand the development of highly selective nanomaterials. This is a paramount challenge in itself. Non-specific sensors can obviate the problems encountered by specific sensors; however, these sensors suffer from low to medium sensitivity. Therefore, obtaining sufficient discrimination between diseased and healthy group might become difficult.

It is therefore clear that in spite of all the prospects that breath analysis brings to the table, developing successful, commercial breath-analysers is fraught with multiple challenges that the researchers world-wide are trying to mitigate.

Potential and Plausible Future of Breath Research

It is beyond doubt that in the near future breath analysis will at least complement if not replace blood-analysis for disease detection. For example, BACtrack is selling "solid oxide fuel cell" based portable breath alcohol analyzer for drunken driving test for 15 years now. Portable halimeters measuring VSCs (Volatile Sulphur compounds, viz. hydrogen sulfide, methylmercaptan, other thiols, and dimethyl sulfide) for the detection of halitosis are available commercially. Portable electrochemical sensor for the detection of trace acetone in exhaled breath is also reported. BOSCH Healthcare Solutions® have already proposed a hand-held breath analyzer for the detection of asthma from exhaled breath. Peak flow meter is a standard technique for the detection of asthma, COPD and other breathing troubles causing shortness of breath.

Dr P. Gouma has demonstrated a diabetic breath analyzer prototype. Ronnie Priefer and Michel Rust, of Western New England University, Springfield, MA and Christine Sleppy, of University of Central Florida have developed similar working protype diabetic breath analysers. Robert Peverall et al. has also come up with a breath acetone detector that uses sample preconcentration and cavity enhanced spectroscopy. However, breath analysis for disease detection is still in its infancy. The future of breath research should be targeted on

- Discovering new biomarkers or set of biomarkers,
- Establishing standard correlations between blood and exhaled breath concentrations of biomarkers, Establishing standard breath collection and storage procedures,
- Differentiating between exogenous and endogenous gases in exhaled breath,
- Developing novel specific nanomaterials for selective detection of breath gases,
- Developing MEMS based miniaturized, portable, low-power devices that use novel, non-specific sensors,
- Reducing the effect of humidity on the sensors,
- Developing simple, repeatable, reproducible, reliable, real-time, light-weight, hand held devices that would be inexpensive,
- Fabricating wearable devices and integrating the technology with Internet of Things (IoT) using preferably smart-phone based applications,
- Reducing the power consumption to such low levels that body-heat, simple exercise or even walking can recharge the battery of the wearable device,
- Proper clinical trial including as many subjects as possible and validation of the prototypes,

On the basis of the above requirements, it seems that the way ahead requires a synergistic endeavor involving researchers of multiple disciplines, such as material researchers, MEMS fabrication specialists, electronics and instrumentation specialists, IoT specialists, and medical doctors.

Conclusions

In conclusion, breath analysis is an interdisciplinary field of research work which includes medical science, analytical techniques, materials chemistry, data processing and electronics. It is a rapidly growing field which can tremendously contribute to the society by early detection of diseases. There exist devices which can be utilized for breath analysis; however, they are bulky, needs trained manpower, costly and not suitable for day to day use. Monitoring of diseases and assessment of exposure to VOCs/gases by analysing exhaled breath using a breathlyzer still has lot of challenges to overcome which includes standardization, sampling methods, defining markers. In particular, moisture of exhaled breath is an important interfaring agent which contributes to sensing and produce erroneous results. A standard, robust and cheap breath-analyzer can come to market for day to day use only when all issues will be resolved.

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